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ORIGINAL ARTICLE

Age-changed normative auditory event-related potential value in children in Taiwan☆

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KEYWORDS
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Background/Purpose: Event-related potentials (ERPs) reflect higher cortical function and the P3 (P300) wave has been associated with various sensory, cognitive, and attention processes. The aims of this study were to understand the age-related change in ERPs in children between the ages of 6 and 13 years and to establish a normal reference value for Taiwanese children for use in future study of neurocognitive dysfunction in children.
Methods: Using an auditory oddball paradigm, ERPs were recorded in 63 mentally and physically normal children ages 6 to 13 years. Parietal, central, and frontal ERP long-latency components (N1, P2, N2, P3) were measured in each test participant.
Results: Linear regression analysis demonstrated a significant linear decrease in P3, P2, N2, and N1 latencies and a significant linear increase in P3, P2, and N1 amplitudes in children between the ages of 6 and 13 years. P3 latency was significantly longer in children ages 6–7 years than in older children. The parietal P3 latency decreases 6.7 msec per year from ages 6 to 13 years. A wide variation in P3 latency in the children ages 6–7 years and a significant increase in P3 amplitude in those ages 12–13 years were observed from our data. A significant increase in P2 amplitude was also observed in children older than 10 years.
Conclusion: The authors conclude that there exists an age-related change in ERP latency and amplitude during childhood. A negative correlation between ERP latencies and age and a positive correlation between ERP amplitude and age were found in this study. The authors

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emphasize that the auditory ERP value in children is not equal to that of adults. A normative auditory ERP value in children should be established prior to clinical application.

Introduction

The recording of event-related potentials (ERPs) from the scalp is a noninvasive technique that provides information regarding neural activity associated with sensory, cognitive, attention, and decision-making processes.[1,2] ERPs have been used as an electrophysiologic tool for studying neural bases of cognitive activities and in clinical application in patients with psychopathologic and neurologic diseases, disorders of learning and attention, dementia, and other cognitive deficits.[1–4]

Auditory stimulus-evoked response is divided into three sequential time periods: early latency, midlatency, and long latency. Whereas the early-latency (less than 10 msec) response (brainstem auditory evoked potentials) reflects activity in peripheral and brainstem auditory structures, the midlatency (10 to 50 msec) response is thought to reflect neural activity arising in thalamocortical radiations of the primary auditory cortex. The long-latency response, i.e., auditory ERP, which starts at approximately 75 msec, and the later slow waves are thought to reflect activity in the limbic system and multiple neocortical regions. ERPs usually are recorded as a series of positive and negative potentials that are maximal at the midline of the centroparietal region. The peaks are named according to the polarity and mean latency in the healthy adult population: in general, major peaks of adult ERPs include N1 (N100), P2 (P200), N2 (N200), and P3 (P300).[3,4]

P3, namely the P300 wave, a late positive waveform, occurs with a latency of approximately 300 msec or more when a study participant attends and discriminates the target from nontarget stimulus in a signal detection task. Neural generators of the P300 wave are unclear, although some evidence has suggested a mesial cortical or subcortical origin.[4–6] In some studies using intracerebral recordings by depth electrodes[6,7] and recording of magnetic fields[8] in humans, it was found that at least part of the P300 is generated in the mesial temporal lobe, most likely in the hippocampus, which is associated with learning and memory. The P300 component has been considered to be associated with different cognitive, linguistic, and attention processes of information, and P300 latency has been reported to be connected with working memory[9–11] and simple problemsolving.[12,13] Abnormalities in the P300 amplitude and/or latency have been linked to learning disabilities, attention deficits, schizophrenia, autism, and other cognitive disorders.[14–17]

Age is an important variable affecting ERPs. Normal data from healthy adults are more stabilized, although a gradual increase in the P300 waveform latency after the age of 25 years has been demonstrated.[18,19] In children the data exhibit more variation than in adults. Studies of ERPs in children using the auditory paradigm have found a decrease in P300 latency with increasing age from 5 years old to young adolescence.[20–22] It is thought that the age-dependent change in the P300 could be related to maturation phenomena in cognitive processes.[22,23] However, most of the studies on the effect of age involve examination of the auditory P300 (P3) waveform. The age-related changes in N1, P2, and N2 waveforms have not been thoroughly studied in children, with the exception of some limited investigations of scalp topography and neural generators in adult studies.[24,25]

Age-related change in the P300 and other ERP waveforms across different age groups in children has not been investigated in Taiwan. Normative studies in children should be conducted before the use of ERPs in clinical applications or further neurocognitive research. The aims of this study were to obtain normative values for the latency and amplitude of each ERP waveform in different age groups of children, and to understand the age-related changes in ERPs and the influence of age and sex in Taiwanese children.

Participants and methods

Participants

Sixty-three mentally and physically normal children (ages 6 to 13 years; 36 males, 27 females) were divided into four age groups for testing: 6–7 years ($n = 18$); 8–9 years ($n = 18$); 10–11 years ($n = 14$); and 12–13 years ($n = 13$). The children had previously visited our outpatient clinics with various acute illnesses or for a health examination unrelated to neurologic or psychiatric illness. Children with impaired hearing, cognitive conditions such as attention deficit hyperactivity disorder, or neurologic conditions such as headache or central nervous system infection were excluded. The tests were performed on healthy children, and informed consent was obtained from their parents or guardians in accordance with the requirement of the ethics boards of the Cathay General Hospital (CGH-CT9762) and Cheng-Hsin General Hospital (CHGH-IRB-165-98-49).

Methods

After cleaning of the skin and scalp, the children were tested in a quiet room while in a relaxed sitting position with their eyes closed. Bioelectrical signals were measured by placing a surface electrode (plate-shape electrode, 11 mm in diameter, Dantec electronic A/S, Denmark) along the midline frontal (Fz), central (Cz), and parietal (Pz) areas according to the 10–20 international system of EEG electrode placement and grounding achieved with a surface electrode located midway between the Fz and midline frontopolar (FPz) points. An electrode was placed infraorbitally to monitor eye movement. A reference electrode

was placed on the mastoid, and the impedance was measured at less than 5 kΩ. The filter band pass was 0.1—50 Hz and the analysis time was 1000 msec. Waveforms were averaged and any electroencephalograms or electro-oculograms greater than 100 μV were automatically rejected.

We applied the "oddball" paradigm of auditory stimulation in this study (Medtronic Keypoint V3.22; Medtronic Functional diagnostic A/S, 2001, Denmark). ERPs were elicited binaurally through headphones with a typical intensity of 60 dB above the hearing level depended upon by the participant. In total, 200 tones were elicited. According to the paradigm, 20% of the tones were "target" (rare), whereas the rest were "nontarget" (frequent), and the delivery sequence of frequent and rare tones was randomized. The target tones were 3000 Hz, whereas the nontarget tones were 2000 Hz; the tone was elicited at a rate of 0.7 Hz. Instructions were given by the technician before the test, with the participant tasked to press the button when they heard a rare tone or count the number of rare tones presented. For the former, the reaction time (RT), i.e., the length of time between emission of the rare tone and button activation, was measured. The test was repeated twice for each participant.

The N1, P2, N2, and P3 latency and amplitude data were determined from the responses to the rare tones (Fig. 1). N1 was defined as the maximal negative peak between 75 msec and 150 msec after stimulus presentation and P2 as the maximal positive peak within the range of 120—250 msec. The N2 ERP was defined as the maximal negative peak between 150 and 350 msec and P3 as the maximal positive peak after N2 within the range of 250—700 msec after stimulus presentation. In the analysis of potentials, the amplitude of P3 was measured from the peak of N2 to the peak of P3 (N2—P3), that of N2 was measured from the peak of P2 to the peak of N2 (P2—N2), that of P2 was measured from the peak of N1 to the peak of P2 (N1—P2), and that of N1 was measured from the first deflection to the peak of N1.[2,26]

Statistical analysis

Mean reference values of the ERP indices (amplitude and latency) in each age group were derived from cross-sectional study. Linear regression analysis and Pearson correlation testing were performed to study the relationship between ERP latencies and amplitudes within in each individual age group. The effects of age and sex were analyzed by analysis of variance (ANOVA) or Student *t*-test. One-way ANOVA and the least significant difference (LSD) *post hoc* test were used for statistical analysis after division into four age groups. Comparisons were considered significant when $p < 0.05$ unless otherwise indicated. All statistical analysis was performed using SPSS (version 17.0; SPSS Inc., Chicago, IL, U.S.A).

Results

Waveform

The ERPs contained recognizable N1, P2, N2, P3 waveform components. Fig. 1 shows the representative waveforms obtained for each electrode in response to both rare and frequent tones using the oddball paradigm auditory stimulation method. The mean latency and amplitude of each ERP component with standard deviation for each age group at the representative Pz electrode are shown in Tables 1 and 2, from which the great variation in P3 latency in the 6- to 7-year age group can be observed.

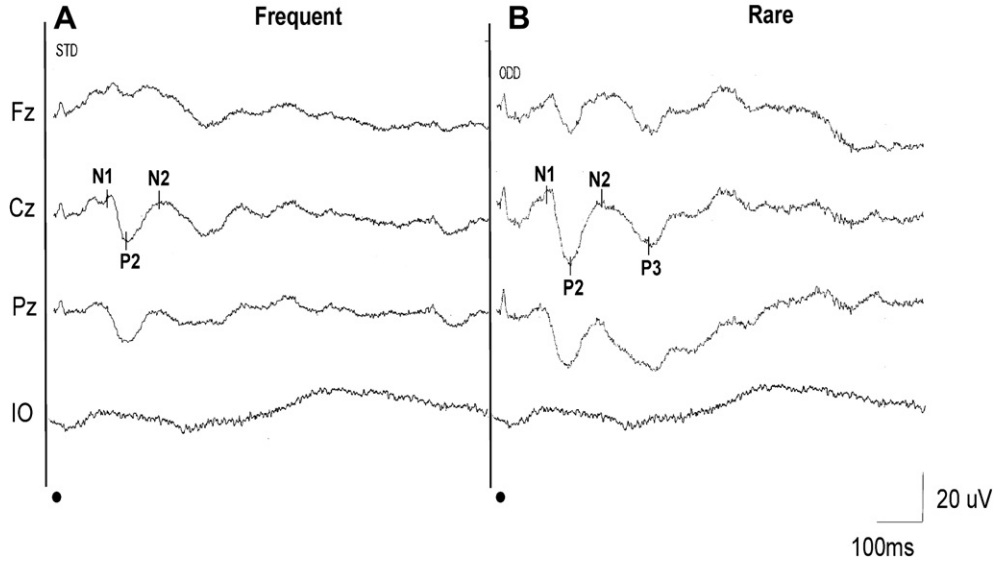

Figure 1 Representative auditory event-related potentials (ERPs) recorded from a 9-year-old healthy boy. (A) ERP responses to the frequent tone. (B) ERP responses to the rare tone. The participant was instructed to press the button as soon as he heard the rare stimuli. Representative ERP waveforms N1, P2, N2, and P3 were observed in three electrodes (Fz, Cz, and Pz). N2 and P3 are more recognizable in the response to rare stimuli. IO = infraorbital electrode. The black filled circles indicate stimulus onset.

Table 1 Event-related potential latencies (msec) in different age groups.[a]

ERP	1. 6—7 years	2. 8—9 years	3. 10—11 years	4. 12—13 years	Total	F value for ANOVA	*p* value for ANOVA	*Post hoc* test
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD			
P3	360.29 ± 61.78	319.11 ± 23.58	323.93 ± 24.65	322.77 ± 22.10	332.70 ± 41.64	4.33	0.008	1 vs. 2* 1 vs. 3* 1 vs. 4*
N2	262.93 ± 45.73	233.03 ± 25.37	231.64 ± 23.06	223.48 ± 12.26	239.65 ± 33.61	5.28	0.003	1 vs. 2* 1 vs. 3* 1 vs. 4*
P2	196.96 ± 47.81	182.40 ± 27.46	170.00 ± 23.89	171.78 ± 12.39	181.54 ± 33.19	2.42	0.075	1 vs. 3* 1 vs. 4*
N1	123.84 ± 28.49	122.76 ± 23.44	98.99 ± 18.02	108.60 ± ± 19.34	114.87 ± 24.90	4.08	0.011	1 vs. 3* 2 vs. 3*

*$p < 0.05$ after the *post hoc* test.
ANOVA = analysis of variance (one-way ANOVA); ERP = event-related potential; SD = standard deviation.
[a] All latency data were recorded at the midline parietal (Pz) location.

Changes in ERP latencies with age

Table 3 shows the linear regression analysis of age-related change in each ERP component at Pz; the intercept, slope, standard error (SE), Pearson correlation coefficient, and *p* value. Fig. 2 shows the scatter plots and linear regression fit lines between age and ERP latencies, from which it can be seen that, as a child grows older, the latencies of P3, N2, P2, and N1 become shorter.

Linear regression analysis demonstrated a significant negative linear correlation of P3 (P300) latency at Pz with age (Table 3, correlation coefficient: -0.35, $p < 0.01$), with a negative slope of -6.66 msec/year and SE of 2.32 msec. The P3 latencies at Fz and Cz also exhibited a significant negative linear correlation with age ($p < 0.05$, data not shown). By ANOVA (Table 1), significant decreases in P3 latency with increasing age at Cz and Pz were observed ($p < 0.05$ and $p < 0.01$, respectively). *Post hoc* LSD testing uncovered a significantly prolonged P3 latency in the 6- to 7-year age group in comparison with older age groups at all electrodes (Table 1). After the age of 8—9 years, P3 latency was more stable, and there was no statistically significant variation among groups between the ages of 8 and 13 years.

A significant negative linear correlations was found between the latencies of N1, P2, and N2 at Pz and age (Table 3, correlation coefficients: -0.34, -0.33 and -0.35, respectively, $p < 0.01$) with negative slopes of -3.89, -5.00, and -6.91 msec/year, respectively (Table 3). The N1, P2, and N2 latencies at Fz and Cz also exhibited significant negative linear correlation with age. By ANOVA (Table 1), a significant decrease in N1 and N2 latency at Pz with age was observed ($p < 0.05$ and $p < 0.01$) in addition to a trend of decreasing P2 latency at Pz with increasing age ($p = 0.075$). *Post hoc* LSD testing uncovered a significant decrease in the N1, N2, and P2 latencies at Pz between the 6- to 7-year age group and the $\geq$ 10 years age group (Table 1). Similar results were obtained for the N1, N2, and P2 latencies at Fz and Cz for the different age groups.

Table 2 Event-related potential amplitudes (μV) in different age groups.[a]

ERP	1. 6—7 years	2. 8—9 years	3. 10—11 years	4. 12—13 years	Total	F value for ANOVA	*p* value for ANOVA	*Post hoc* test
	mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD			
P3	12.90 ± 3.83	14.88 ± 4.37	15.89 ± 4.66	19.99 ± 5.60	15.59 ± 5.18	6.08	0.001	4 vs.1* 4 vs.2* 4 vs.3*
N2	11.30 ± 4.07	10.54 ± 3.97	13.25 ± 4.65	12.27 ± 5.45	11.74 ± 4.45	1.13	0.343	
P2	8.96 ± 3.42	11.43 ± 3.83	19.11 ± 4.20	20.66 ± 4.87	14.41 ± 6.39	32.28	<0.001	3 vs.1* 3 vs.2* 4 vs.1* 4 vs.2*
N1	9.61 ± 4.38	10.77 ± 4.74	11.02 ± 3.51	12.73 ± 4.80	10.90 ± 4.43	1.27	0.293	

*$p < 0.05$ after the *post hoc* test.
ANOVA = analysis of variance (one-way ANOVA); ERP = event-related potential; SD = standard deviation.
[a] All amplitude data were recorded at the midline parietal location (Pz), with the exception of P3, which was measured at the midline central (Cz) location.

Table 3 Linear regression analysis of age-related variation in event-related potential latencies and amplitudes in 6- to 13-year-old healthy children.[a]

	Latency				Amplitude			
	Intercept (msec)	Slope (msec/year)	SE about regression line (msec)	Correlation coefficient	Intercept (μV)	Slope (μV /year)	SE about regression line (μV)	Correlation coefficient
P3	394.58	-6.66	2.32	-0.35**	7.53	0.82	0.29	0.34**
N2	303.45	-6.91	1.79	-0.44***	8.97	0.30	0.26	0.15
P2	227.97	-5.00	1.86	-0.33**	-6.58	2.26	0.24	0.76***
N1	151.01	-3.89	1.39	-0.34**	6.01	0.53	0.25	0.26*

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
SE = standard error.
[a] All latency data were recorded at the midline parietal (Pz) location.

Changes in amplitude with age

Fig. 3 shows the scatter plots and linear regression fit lines between age and ERP amplitudes, and Table 2 shows the amplitude in μV/year for each waveform with their SE. The P3 amplitude at Pz exhibited a significant positive linear correlation with age (correlation coefficient 0.34, $p < 0.01$), with a positive slope of 0.82 μV/year and a SE of 0.29 μV (Table 3). The P3 amplitude at Fz and Cz showed a similar significant linear correlation with age ($p < 0.01$). By ANOVA, a significant increase in P3 amplitude at Fz, Cz, and Pz with age was uncovered ($p < 0.01$, $p < 0.01$, and $p = 0.08$, respectively). *Post hoc* LSD testing revealed a significant increase in P3 amplitude in the children ages 12—13 years in comparison with the other age groups ($p < 0.05$, Table 2).

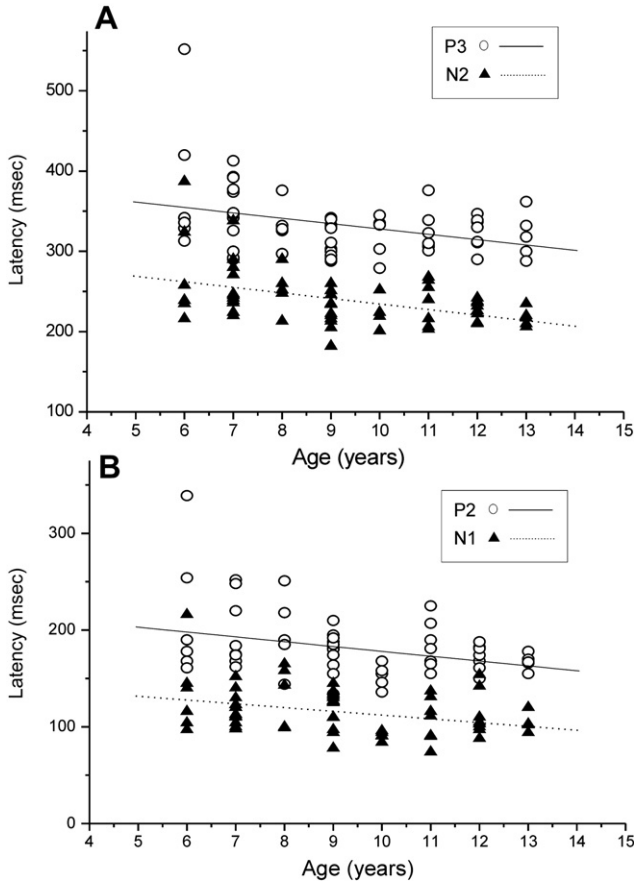

Figure 2 Effect of age on the latencies of event-related potentials (ERPs). The lines represent the regression lines from our data obtained from 63 healthy children ages 6—13 years. The latency of each component decreased with age. (A) P3 latency (open circles, solid line) decreases by 6.66 msec/year and N2 latency (solid triangles, dotted line) by 6.91 msec/year. (B) P2 latency (open circles, solid line) decreases by 5.00 msec/year and N2 latency (solid triangles, dotted line) by 3.89 msec/year.

Linear regression analysis demonstrated a significant positive correlation in the amplitudes of N1 and P2 at Pz with age (correlation coefficients: 0.26 and 0.76, $p < 0.05$ and $p < 0.001$, respectively) with a positive slope of 0.53, 2.26 μV/year (Table 3). The N1, P2, and N2 amplitudes at Fz and Cz showed a similar significant positive linear correlation with age. A robust increase in P2 amplitude was observed at age 10 years, whereas ANOVA showed a significant increase in P2 amplitude at Fz, Cz, and Pz in the ≥ 10 years age group in comparison with the younger age groups ($p < 0.001$, ANOVA with LSD *post hoc* test, Table 2). Fig. 4 demonstrates the higher amplitudes and shorter latencies of P2 and P3 in 11- and 13-year-old representative children. P2 amplitudes were higher in the 11- and 13-year-old children in comparison with other age groups, and a longer latency of P2 was observed in the 7- and 9-year-old children (Fig. 4, arrows). ANOVA did not find a significant difference between the amplitudes of N1 and N2 for different age groups (Table 2).

Reaction time

RT was recorded in 44 children. A highly significant negative correlation between RT and age was found (correlation coefficient -0.71, $p < 0.001$), and RT was observed to be significantly correlated with the latencies of P3 and N2 (correlation coefficients 0.46 and 0.35 and $p < 0.01$ and $p < 0.05$, respectively) but not the latencies of P2 and N1. The percentage of children with a RT shorter than the peak latency of P3 was 25% (11 of 44), all of whom were older than 9 years.

Sex effect

We did not find a sex difference in the latencies and amplitudes of each ERP waveform, with the exception that

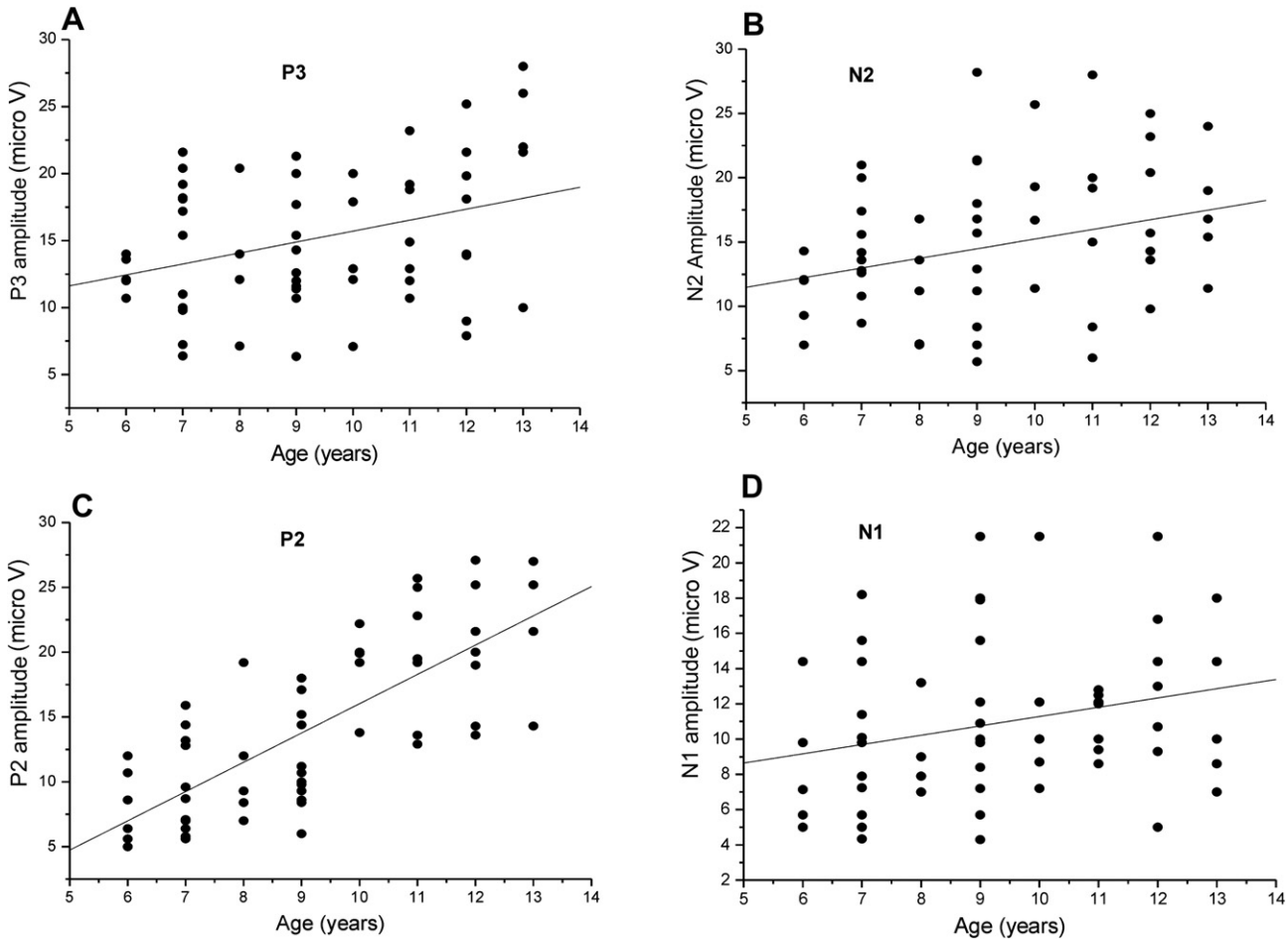

Figure 3 Effect of age on the amplitude of event-related potentials (ERPs). The solid lines represent the regression lines of the amplitude with age. The amplitude of each component increased with age. (A) P3 amplitude at Pz increased by 0.82 μV/year. (B) N2 amplitude at Cz increased by 0.75 μV/year. (C) P2 amplitude at Pz increased by 2.26 μV/year. (D) N1 amplitude at Pz increased by 0.53 μV/year.

the P3 latency at Pz and the N2 latency at Fz were increased in girls ($p < 0.05$). No significant sex differences in latency and amplitude were observed among each age group.

Discussion

Auditory ERP and P300 studies have been widely used in recent decades as a noninvasive method to evaluate the function of cognition and attention in children. The normal values of ERPs in children and evaluation of the age-related changes in ERPs have not been reported in Taiwan. In this study, the different components of ERPs in children age 6-13 years were identified. A significant negative correlation of ERP latency and a positive correlation of ERP amplitude with age were found. The major findings of this study were as follows: N1, P2, N2, and P3 latencies gradually decreased with age, while P2, N2, and P3 amplitudes gradually increased with age; P3 latency significantly decreased after age 8—9 years with a slope of -6.7 ms/year, and P3 amplitude increased at age 12—13 years with a slope of +0.82 μV/year; a robust increased P2 amplitude was found after age 10 years, and this finding has rarely been mentioned in the past reports; no sex effect was observed in this study.

Latency

P3 and N2 are the most sensitive ERP components in cognitive processes and are associated with rare attended tones reflecting short-term memory, problem-solving, and decision-making processes.[2] The results of this study showed that the components of auditory ERPs vary in a systemic pattern in children between the ages of 6 and 13 years. Although ERPs have been studied in children younger than 6 years,[27] we excluded participants younger than 6 years because the greater latency variability in younger children may confound our data analysis. Our data are consistent with the results of previous studies showing that P3 and N2 latencies decrease with age. Some studies have shown that P3 latency decreases to the minimum value in adolescence at approximately 18 years of age.[18,19,21] Decreased slopes of P3 latency ranging from 3.6 to 18.4 cm/year in children have been reported in various

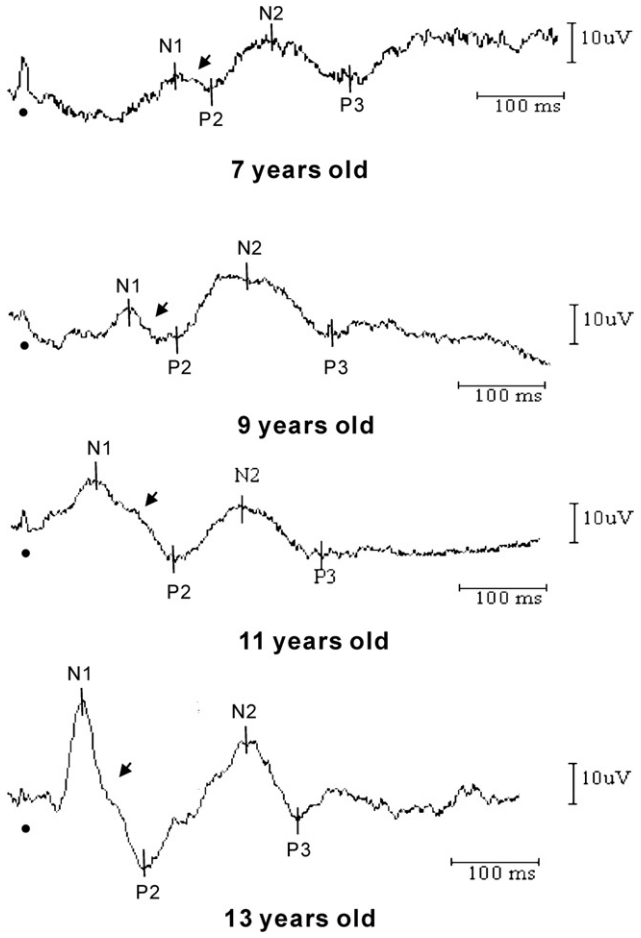

Figure 4 Representative auditory event-related potentials (ERPs) for different age groups. These ERP examples are for rare (target) stimuli at the Pz in an auditory oddball paradigm. A gradual decrease in P2 and P3 latencies from ages 7—13 years was observed, and an increase in the P2 (N1—P2) amplitude was seen in children ages 11—13 years, compared with a small amplitude for P2 in children age 7— 9 years (arrows). Black filled circles indicate stimulus onset.

studies.[10,18,23] In our study, a decrease of 6.7 msec/year in P3 latency at Pz was observed. A rather steady P3 latency followed by a slow age-related increase in P3 latency during adulthood have also been documented.[18,21]

Our data demonstrated a significant decrease in P3 latency between the ages 6-13 years, and a significantly longer P3 latency was observed in the 6— and 7-year-olds as compared with the children age 8—9 years and older. In general, most studies agree that P3 latency and amplitude reach the mature values by puberty or young adulthood.[12,18] Our data indicated a shorter P3 latency (360 ± 62 msec) in comparison with other reports, in which the value ranges from 400 to 500 msec in 6-to 7-year-olds.[20,21,24] The reason for this difference may be variation in the methodology used for ERP collection (for example, the frequency of the sound stimuli) between studies. Greater variability in P3 latency in younger children was also shown in this study.

The latencies of N1, N2, and P2 exhibited a significant decline with increasing age. In contrast with N1 and P2 waveforms, N2 and P3 are considered to be endogenous ERPs.[25] Controversy exists over the N1—P2 component: Courchesne[28] described the N1—P2 component as exogenous, whereas Oken[29] regarded it as endogenous in a separate review article, and Polich et al.[10] interpreted the change in the N1—P2 component as a reflection of sensory function rather than cognitive function. Age-related changes in N1 and P2 have been reported from childhood to adolescence,[18,28] and our findings are in agreement with previous reports; however, some studies have not found significant changes in N1 and P2 from childhood to adulthood.[24,30]

Amplitude

The amplitudes of P3, N2, and P2 were found to increase in children ages 6-13 years in this study (Tables 2and 3), which is in agreement with previous reports.[10,18,24] The P3 amplitude was found to be significantly increased in the children ages 12—13 years in our study. However, the amplitude of P3 decreases slightly after around the age of 13 years to a normal adult value.[10] A robust increase in the amplitude of the N1—P2 (P2) component was observed in children older than 10 years ($p < 0.01$) in our study (Table 2 and Fig. 4). Taken together with the observation of a decreasing trend in the latency of P2 in the 10- to 11-year age group in comparison with the 8- to 9-year-olds ($p = 0.075$), these results were in agreement with those of Courchesne,[21] suggesting that 10 years of age is a point of maturation of myelination and sensory function.[21,28]

Reaction time

RT is the time required for impulses to travel from the brain out to the muscles and represents the decision process that evokes response. Previous reports have shown that the P300 latency and amplitude may reflect the temporal course of decision-making, as assessed by RT measurement.[31—33] Our results showed that RT was highly correlated with the endogenous ERP latencies of P3 and N2 (correlation coefficients 0.46 in P3, $p < 0.01$ and 0.35 in N2, $p < 0.05$) but not the latencies of P2 and N1, which was in agreement with previous studies demonstrating that RT corresponds with the latencies of P3 and N2.[12,33] However, when speed was emphasized, RT could occur earlier than P3 latency.[31]

Conclusion

We conclude that age-related change exists in ERP latency and amplitude. A negative correlation between ERP latencies and age, and a positive correlation between ERP amplitude and age were found in this study. Given the great age-related variation of P3 latencies in children, ERP data should be interpreted very carefully and cautiously in children of different ages, and the clinical application of ERP latencies for children in this age range should be supported by psychologic and neurologic evaluation.

Acknowledgments

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